p53 function can lead to uncontrolled proliferation of cells and tumor growth. Although loss of p53 activity may or may not, by itself, be the trigger to transforming a cell into a cancer cell, it is well recognized that detectable cancers are more common and likely to grow in persons with p53 mutations. In fact, mutants of p53 are the most common genetic aberration for many types of cancer (specification at page 1). As is elaborated in detail on page 2 of the specification, p53 activity is highly dependent upon the ability of the protein to maintain its functional conformation. However, analysis of p53 from the cells of many tumors reveals that the DNA binding domain thereof is frequently mutated. Specific residue positions in p53, known as hot spots, are mutated at unusually high frequencies in cells evidencing major cancer (specification at page 2).

Generally speaking, mutant p53 proteins are not as stable as wild type protein, having shorter effective lifetimes and/or less inherent regulatory activity. In the current state of the art, efforts have focused on replacing such defective p53 protein molecules by gene therapy in order to provide a wild-type encoding nucleotide sequence. The present Specification discloses a completely different approach demonstrating, for example, that small molecule drugs can rescue a functional conformation in defective p53. The present invention thus has broad implications for cancer therapy. In the text of the present application, Applicant has provided actual data from an art-recognized *in vivo* model (suppression of human tumor cells transplanted into nude mice) clearly showing operability of the invention. See, for example, page 12 of the application referring to Figure 6, showing testing of compound "X", N-{2-[2-(4-Methoxy-phenyl)-vinyl]-quinazolin-4-yl}-N',N'-dimethyl-propane-1,3-diamine hydrochloride. The species referred to as compound "X" is depicted in Figure 2 of the Specification, and is also the subject of *in vivo* model Example 4 (pages 49-50), and Figures 5 and 6 (see pages 11-12)..

Applicant has thus demonstrated that the conformation of mutant p53 can be stabilized by administration of an organic non-peptide compound. With respect to compound X, Applicant has further demonstrated that stabilizing the conformation of mutant p53 results in enhanced p53 function (Example 3 on page 47). Referring to pages 41 and 49-50 of the Specification, p53 possesses an epitope recognized by monoclonal antibody mAb1620. The epitope is conformation-dependent, and the epitope's presence correlates strongly with p53's tumor suppressor activity. In Example 4 (page 49-50), Applicant demonstrated that p53 function can be stabilized in human tumor cells that express mutant p53, and which are being cultured in nude mice. Figure 6 demonstrates that human tumor xenografts (in nude mice) can be suppressed by administration of a compound useful in the practice of the invention. The tumor cells express mutant p53, and upon administration of compound, tumor volumes decrease. Simply stated, Applicants have provided very remarkable experimental results, which are now published at Science, v. 286, pp. 2507-2510, and Cancer Biology and Therapy, Internet pre-published on September 4, 2001 as Manuscript MS# 08-08-01 (note that the compound identified therein as CP-31398 is compound X of the present application).

The section 112 rejections

The Examiner has rejected the pending claims under 35 USC section 112, first paragraph, generally on the grounds that one skilled in the art could not use the entire scope of the claimed invention without undue experimentation. The rejection is respectfully

traversed. The scientific journal articles made of record herewith generally establish:

(1) that the meaning of the term cancer is well recognized;

(2) that a wide and known variety of tumor types express abnormalites with respect to proteins of the p53 family; and

(3) that it is well established dogma among those skilled in the art that proper function of p53 should prove useful in the treatment of cancers, if only proper function could be reestablished.

In this regard, the Examiner's attention is directed to the following aspects of some of the newly cited references. The *Hollstein et al.* reference, for example, is representative of publications showing the wide occurence of p53 mutations in a diverse variety of human tumor types. The *Bullock et al.* reference (recently published in 2001) discusses the value of rescuing p53 function (which is described as the nemesis of MOST cancers, see the opening summary on page 68, emphasis added). The *Bullock et al.* reference also discusses the present Applicants' work at length (see pages 73-74). The *Smith et al.* reference also supports the widely recognized value of p53-mediated therapy against cancer.

The Examiner's attention is also directed to the *Pennisi* reference which discusses the wide application of the present developments to a very wide variety of cancers. Finally the previously mentioned Takimoto et al. reference (of authors collaborating with Applicants) demostrates arrest of a wide variety of cancer cell types. Accordingly, it is believed that the rejection is overcome.

The Examiner has rejected the pending claims under 35 USC section 112, first paragraph, on the grounds that the Specification does not sufficiently enable the term "organic non-peptide compound". The term "organic non-peptide compound" is intended to distinguish, for example, use of what may be natural protein/peptide ligands of p53, or synthetic peptides, or antibodies. It is believed that the term is sufficienty defined, for example, on page 17 of the Specification, so that those skilled in the art would find it clear. Applicants respectfully advance their belief that the present invention is pioneering (as evidenced by its reception in the scientific community, see above) and represents a completely different approach to cancer therapy than could be predicted from the prior art. Accordingly, Applicants are entitled to a broad claim. In regard of this, the Specification discloses a very wide variety oforganic compounds that come within the definition of "organic non-peptide compounds", and that are useful in the practice of the invention. In fact, pages and pages and pages of compounds are disclosed, thereby directly guiding the reader to the structures of additional compounds useful in the practice of Applicants' method claims.

The Examiner's rejection under 35 USC section 112, second paragraph, has been made moot, at least in part, by the cancelation of most of the affected claims. However, the Examiner is asked to clarify the remainder of the rejection, particularly with respect to the requirement that the claims recite the actual amounts of compounds to be employed. It is believed that standard United States practice requires, at best, only generic use of the term "an effective amount", with guidance thereto being provided, as is presently the case, in the text of the Specification.

Conclusion

The Examiner is welcome to contact the undersigned to discuss the application. A Petition for Extension of Time (3 months) is attached in duplicate, as is a Supplementary Information Disclosure Statement, also in duplicate, with fee authorization. The Patent Office is authorized to charge any fee deficiency, or credit any overpayment, to Deposit Account 16-1445.

Respectfully submitted,

Date: 1/14/02

E. Victor Donahue, Ph.D.
Attorney for Applicant(s)
Reg. No. 35,492

Pfizer Inc Legal Department,
150 East 42nd Street, 5th floor
New York, NY 10017-5612
(212) 733-2739